Amendments to the Specification:

At page 1, lines 2-6, please replace the "CROSS-REFERENCE TO RELATED APPLICATIONS" paragraph with the following amended paragraph:

This application is a continuation of U.S. Application Serial No. 10/035,397, filed October 25, 2001, now U.S. Patent No. 6,887,462, which claims the benefit of U.S. Provisional Application Serial No. 60/330,404, filed October 18, 2001, and U.S. Provisional Application Serial No. 60/282,614, filed April 9, 2001, each of which is herein incorporated by reference in its entirety.

Please replace the paragraph at page 14, line 20, continuing through page 15, line 3, with the following amended paragraph:

The stabilized pharmaceutical formulations of the invention comprise IFN-β and variants thereof. The term "IFN-β" as used herein refers to IFN-β or variants thereof, sometimes referred to as IFN-β-like polypeptides. Human IFN-β variants, which may be naturally occurring (e.g., allelic variants that occur at the IFN-β locus) or recombinantly produced, have amino acid sequences that are the same as, similar to, or substantially similar to the mature native IFN-β sequence shown in SEQ ID NO:1. Fragments of IFN-β or truncated forms of IFN-β that retain their activity are also encompassed. These biologically active fragments or truncated forms of IFN-β are generated by removing amino acid residues from the full-length IFN-β amino acid sequence using recombinant DNA techniques well known in the art. IFN-β polypeptides may be glycosylated or unglycosylated, as it has been reported in the literature that both the glycosylated and unglycosylated IFN-β's show qualitatively similar specific activities and that, therefore, the glycosyl moieties are not involved in and do not contribute to the biological activity of IFN-β.

Please replace the paragraph at page 15, lines 4-19, with the following amended paragraph:

The IFN-β variants encompassed herein include muteins of the mature native IFN-β sequence shown in SEQ ID NO:1, wherein one or more cysteine residues that are not essential to biological activity have been deliberately deleted or replaced with other amino acids to eliminate sites for either intermolecular crosslinking or incorrect intramolecular disulfide bond formation. IFN-β variants of this type include those containing a glycine, valine, alanine, leucine, isoleucine, tyrosine, phenylalanine, histidine, tryptophan, serine, threonine, or methionine substituted for the cysteine found at amino acid 17 of the mature native amino acid sequence. Serine and threonine are the more preferred replacements because of their chemical analogy to cysteine. Serine substitutions are most preferred. In one embodiment shown in SEQ ID NO:2, the cysteine found at amino acid 17 of the mature native sequence shown in SEQ ID NO:1 is replaced with serine. Cysteine 17 may also be deleted using methods known in the art (see, for example, U.S. Patent No. 4,588,584, herein incorporated by reference), resulting in a mature IFN-β mutein that is one amino acid shorter than the mature native IFN-β. See also, as examples, U.S. Patent Nos. 4,530,787; 4,572,798; and 4,588,585. Thus, IFN-β variants with one or more mutations that improve, for example, their pharmaceutical utility are also encompassed by the present invention.

At page 17, please replace the paragraph beginning on line 9 and continuing through line 2, page 18, with the following amended paragraph:

Thus, the determination of percent identity between any two sequences can be accomplished using a mathematical algorithm. One preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller (1988) *Comput. Appl. Biosci.* 4:11-7. Such an algorithm is utilized in the ALIGN program

(version 2.0), which is part of the GCG alignment software package. A PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used with the ALIGN program when comparing amino acid sequences. Another preferred, non-limiting example of a mathematical algorithm for use in comparing two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 90:5873-5877, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci USA* 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST amino acid sequence searches can be performed with the XBLAST program, score = 50, wordlength = 3, to obtain amino acid sequence similar to the polypeptide of interest. To obtain gapped alignments for comparison purposes, gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402. Alternatively, PSI-BLAST can be used to perform an integrated search that detects distant relationships between molecules. See Altschul *et al.* (1997) *supra*. When utilizing BLAST, gapped BLAST, or PSI-BLAST programs, the default parameters can be used. *See* ~~http://www.ncbi.nlm.nih.gov~~ the website ncbi.nlm.nih.gov available on the world wide web. Also see the ALIGN program (Dayhoff (1978) in *Atlas of Protein Sequence and Structure* 5:Suppl. 3, National Biomedical Research Foundation, Washington, D.C.) and programs in the Wisconsin Sequence Analysis Package, Version 8 (available from Genetics Computer Group, Madison, Wisconsin), for example, the GAP program, where default parameters of the programs are utilized.

Please replace the paragraph at page 18, line 20, continuing through page 19, line 2, with the following amended paragraph:

Biologically active variants of IFN-β encompassed by the invention should retain IFN-β activities, particularly the ability to bind to IFN-β receptors. In some embodiments, the IFN-β variant retains at least about 25%, about 50%, about 75%, about 85%, about 90%, about 95%, about 98%, about 99% or more of the ~~biologically~~biological activity of the polypeptides whose amino acid sequences are given in ~~Figure 1 or 2~~SEQ ID NO:1 or 2. IFN-β variants whose

activity is increased in comparison with the activity of the polypeptides shown in ~~Figure 1 or 2~~ SEQ ID NO:1 or 2 are also encompassed. The biological activity of IFN-β variants can be measured by any method known in the art. Examples of such assays can be found in Fellous *et al.* (1982) *Proc. Natl. Acad. Sci USA* 79:3082-3086; Czerniecki *et al.* (1984) *J. Virol.* 49(2):490-496; Mark *et al.* (1984) *Proc. Natl Acad. Sci. USA* 81:5662-5666; Branca *et al.* (1981) *Nature* 277:221-223; Williams *et al.* (1979) *Nature* 282:582-586; Herberman *et al.* (1979) *Nature* 277:221-223; Anderson *et al.* (1982) *J. Biol. Chem.* 257(19):11301-11304; and the IFN-β potency assay described herein (see Example 2).

At page 21, please replace the paragraph at lines 6-22 with the following amended paragraph:

The recombinantly produced IFN-β for use in preparing the stabilized HSA-free IFN-β pharmaceutical compositions of the invention can be recovered and purified using any method known to one of skill in the art. Such methods include those disclosed in U.S. Patent Nos. 4,462,940 and 5,702,699, herein incorporated by reference. These methods recover the interferon in a pure form of IFN-β that tends to form aggregates in the absence of SDS, which is used as a solubilizing agent. Further, these methods expose the protein to high pH conditions that may adversely affect the protein's biological properties, and can result in compositions containing residual amounts of SDS used to solubilize the protein during purification. Thus, while the IFN-β may be obtained using these methods, preferably it is recovered and purified by the improved method disclosed in the copending provisional application entitled "*Improved Method of Protein Purification and Recovery*," filed October 27, 2000, and assigned U.S. Application Serial No. 60/243,965, copending provisional application entitled "*Improved Method of Protein Purification and Recovery*," filed April 9, 2001, and assigned U.S. Application Serial No. 60/282,607, and the provisional application filed concurrently herewith entitled "*Methods of Protein Purification and Recovery*," and assigned U.S. Application Serial ~~No.~~ ~~No.~~ 60/330,375; the contents of which are herein incorporated by reference in their entirety.

At page 33, please replace the paragraph at lines 19-25 with the following amended paragraph:

Purified IFN-β-1b (1 L of 1.91 mg/ml in 0.4% SDS, 50 mM acetate buffer, pH 5.5) was stored at 5°C. During storage, some of the SDS present precipitated. 250 ml of this material (477.5 mg) was mixed with 229 g of guanidine hydrochloride (6 M, total volume 400 ml) and stirred at room temperature for 15 minutes using a magnetic stir bar. The 6 M guanidine hydrochloride/protein solution was then filtered with a Sartobran® P Capsule (cellulose acetate membrane filters, 0.45μm pore size) to remove the precipitated SDS. The protein concentration as determined by UV at 280 nm was 1.02 mg/ml. The protein yield was 406 mg or 85%.

At page 33, please replace the paragraph at lines 26-30 with the following amended paragraph:

The 400 ml guanidine-hydrochloride treated material was concentrated utilizing a Millipore® Labscale® TFF diafiltration system (high performance, tangential flow filtration cassette and system; Millipore, Inc.) with two Pellicon® XL Biomax® 0.1 cm^2 10 kD polysulfone (polyethersulfone) membranes (Millipore, Inc.). The volume following the concentration step was 37 ml with a protein concentration of 10.3 mg/ml for a post concentration yield of 381 mg or 93%.

At page 34, please replace the paragraph at lines 1-12 with the following amended paragraph:

Using a transfer pipette, 10 ml (103 mg) of the concentrated guanidine hydrochloride/protein solution were gradually added to 590 ml of 5 mM glycine, pH 3.2 solution. The buffer was at a rapid stir using a magnetic stir bar; the protein solution was added

directly to the vortex. This 60X dilution of the 6 M guanidine hydrochloride/protein solution yielded a 0.1 M guanidine hydrochloride/protein solution at 0.17 mg/ml. This 600 ml was transferred to a 500 ml scale diafiltration unit equipped with two Pellicon® II 10kD, 0.1 m^2 polysulfone (polyethersulfone) membranes. This solution was initially concentrated to ~400mL to a protein concentration of 0.23 mg/ml, and subsequently diafiltered against 9 volume changes (3.6 L) of 5 mM glycine at pH 3.2. The final diafiltrate (402 ml) was measured by UV at 280 nm for a final protein concentration of 0.23 mg/ml with a 92.46 mg or 90% yield for the diafiltration step and an overall yield of 72% soluble protein for the purification process.